

# Insulin resistance syndrome as a feature of cardiological syndrome X in non-obese men

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## Abstract

**Objective**—To assess the features of the insulin resistance syndrome in patients presenting with cardiological syndrome X, who experience angina despite angiographically normal coronary arteries.

**Patients and methods**—14 Non-obese male patients with syndrome X and 38 symptom free, apparently healthy, male volunteers were studied. Insulin sensitivity (inversely related to insulin resistance) was measured by minimal modelling analysis of glucose and insulin concentrations during an intravenous glucose tolerance test. Serum lipids, lipoproteins, and apolipoproteins were also measured.

**Results**—Insulin sensitivity was 31% lower in the men with syndrome X ( $p < 0.05$ ) and fasting insulin concentration was 30% higher ( $p < 0.05$ ). The patient group also had 64% higher mean triglycerides ( $p < 0.001$ ) and 20% lower mean high density lipoprotein cholesterol concentration ( $p < 0.01$ ). Systolic blood pressure was also 10% higher in the syndrome X group ( $p < 0.01$ ). There were no differences in total cholesterol, low density lipoprotein cholesterol or lipoprotein (a).

**Conclusion**—These findings show that non-obese male patients with anginal chest pain but normal coronary arteries (syndrome X) are insulin resistant, hyperinsulinaemic, and have higher concentrations of triglycerides and lower high density lipoprotein cholesterol than healthy men. The insulin resistance syndrome may predispose to a spectrum of arterial disease capable of causing myocardial ischaemia.

(Br Heart J 1994;71:41-44)

abnormalities within the blood or myocardium resulting in ischaemia,<sup>3</sup> and reduced blood flow secondary to either microvascular disease<sup>4,5</sup> or alterations in vasomotor tone.<sup>6</sup>

Recently, the combination of insulin resistance, hyperinsulinaemia, high plasma triglyceride concentration, low high density lipoprotein (HDL) cholesterol concentration, and raised blood pressure has also, confusingly, been labelled syndrome X.<sup>7</sup> Insulin resistance seems to underlie these related disturbances in risk factors for coronary heart disease and the term insulin resistance syndrome may be more appropriate.

As hyperinsulinaemia has also been implicated in the pathogenesis of cardiological syndrome X,<sup>8</sup> we investigated a group of patients with syndrome X angina to see if they had the insulin resistance syndrome.

## Patients and methods

### PATIENTS

Fourteen non-obese, white, male patients of mean age 46.6 (range 31-59) years were selected after review of cardiac catheterisation and case records. All patients reported a history of chest pain typical of angina pectoris, with electrocardiographic evidence of ischaemia on exercise but normal coronary arteries at angiography. Coronary arteriograms were considered normal if there were no stenoses on visual inspection by two experienced observers. An exercise test was performed to the Bruce protocol and considered positive for ischaemia if ST segment depression  $> 1$  mm developed in any leads at peak exercise. Patients were excluded if they had taken any drugs known to affect lipid or carbohydrate metabolism in the previous 6 months, if there was any evidence of structural heart disease, or if they deviated by more than 20% from their ideal body weight (Metropolitan Life tables<sup>9</sup>).

### CONTROLS

Thirty eight apparently healthy and clinically normal, male, white, volunteers of mean age 47.3 (range 30-60) years were also studied. They were seen as part of a medical health screening programme and none had any symptoms suggestive of heart disease. Physical examination and resting electrocardiogram were normal in each case. They were also selected to be within 20% of their ideal body weight and were taking no medication known to affect lipid or carbohydrate metabolism.

Cardiologists use the term syndrome X to refer to patients who present with anginal chest pain, are found to have a positive exercise electrocardiogram suggestive of myocardial ischaemia, but no angiographic evidence of atherosclerotic coronary artery disease.<sup>1</sup> The pathological mechanisms responsible for the chest pain in this condition, which was originally described by Kemp,<sup>2</sup> remain obscure. In the absence of stenoses of a coronary artery, various theories have been proposed to explain the origin of the symptoms. These include biochemical

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Accepted for publication  
23 August 1993.

Table 1 Population characteristics

	Syndrome X	Controls
Age (yr)	46.6 (2.4)	47.3 (1.5)
Height (m)	179 (2.5)	176 (1.2)
Weight (kg)	80.0 (2.5)	76.4 (1.4)
Body mass index (kg/m <sup>2</sup> )	24.8 (0.6)	24.5 (0.3)
Systolic blood pressure (mm Hg)	130 (4.0)	118 (2.2)
Diastolic blood pressure (mm Hg)	78 (3.0)	75 (1.5)
Current smokers (%)	7	27
Previous smokers (%)	64	60

Values are mean (SEM).

Table 2 Lipids and lipoproteins

	Syndrome X	Controls	p Value
Total cholesterol (mmol/l)	5.17 (0.26)	5.14 (0.13)	NS
Triglyceride (mmol/l)*	1.56 (+0.26, -0.23)	0.95 (+0.08, -0.07)	<0.001
HDL cholesterol (mmol/l)	1.01 (0.07)	1.27 (0.05)	<0.01
HDL <sub>3</sub> cholesterol (mmol/l)	0.75 (0.04)	0.91 (0.03)	<0.01
HDL <sub>2</sub> cholesterol (mmol/l)	0.26 (0.04)	0.36 (0.03)	<0.05
LDL cholesterol (mmol/l)	3.33 (0.21)	3.38 (0.12)	NS
Apolipoprotein AI (mg/dl)	115 (5.4)	138 (3.4)	<0.001
Apolipoprotein B (mg/dl)	76 (4.5)	77 (3.0)	NS
Lipoprotein (a) *(mg/dl)	6.6 (+3.0, -2.1)	5.9 (+1.6, -1.3)	NS

\*Log transformed data result in asymmetric SEMs. Values are mean (SEM).

The study protocol was approved by the Ethics Committee of the Wynn Institute for Metabolic Research. All volunteers gave written informed consent.

#### STUDY PROTOCOL

After an overnight fast, all participants attended the Wynn Institute, having eaten a high carbohydrate diet (>200 g carbohydrate/day) for three days before admission. Fasting blood samples were taken for serum lipid and lipoprotein assays and this was followed by a three hour intravenous glucose tolerance test (IVGTT). Blood was sampled through an indwelling cannula positioned in an antecubital vein. For the IVGTT a glucose load of 0.5 g/kg body weight was injected through a cannula in the other arm after taking baseline samples for glucose, insulin, and C-peptide. Subsequent samples were taken at 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180 minutes. These were immediately placed on ice and centrifuged within 15 minutes.

#### ASSAYS

Plasma glucose was measured within six hours by a glucose oxidase technique.<sup>10</sup> Plasma insulin and C-peptide were measured on samples stored at -20°C with double antibody radioimmunoassays (Guildhay, UK). Total cholesterol and triglyceride were measured with fully enzymatic assays. The HDL cholesterol was measured after heparin manganese precipitation of other lipoproteins,<sup>11</sup>

then the HDL<sub>3</sub> subfraction was measured after further precipitation with dextran sulphate.<sup>12</sup> The HDL<sub>2</sub> subfraction was calculated as the difference between HDL and HDL<sub>3</sub>. Low density lipoprotein (LDL) cholesterol was calculated from the Friedewald formula.<sup>13</sup> Apolipoproteins AI and B were measured by immunoturbidimetry<sup>14</sup> and lipoprotein (a) by an enzyme linked immunosorbent assay (ELISA) method (Biopool, Sweden).

#### ANALYSIS DATA

Incremental glucose, insulin, and C-peptide areas (the area between the fasting concentration and the profile curve) were calculated by the trapezium rule. Incremental insulin and C-peptide areas were further divided into first phase (0–10 min) and second phase (10–180 min).

Insulin sensitivity was assessed with the minimal model approach of Bergman.<sup>15</sup> This computer modelling approach estimates the variables that best account for the glucose concentrations found when the insulin values are supplied as input. The model gives an index of insulin sensitivity (S<sub>i</sub>) that is a measure of the fractional increase in glucose uptake due to the increase in insulin concentration during the IVGTT and is inversely related to insulin resistance.

Effective use of the model depends on there being a sufficient pancreatic insulin response to injected glucose. Although others have used tolbutamide or insulin injection to achieve this end, we use an increased dose of glucose (0.5 g/kg v 0.3 g/kg used by others) and have found this to be effective,<sup>16</sup> providing measures of insulin sensitivity that correlate well with those from the euglycaemic clamp ( $r = 0.92$ ,  $p < 0.001$ , Swan *et al.*, in press).

The distribution of each variable was examined and normalised by appropriate transformation. The groups were compared with unpaired two tailed Student's *t* tests.

#### Results

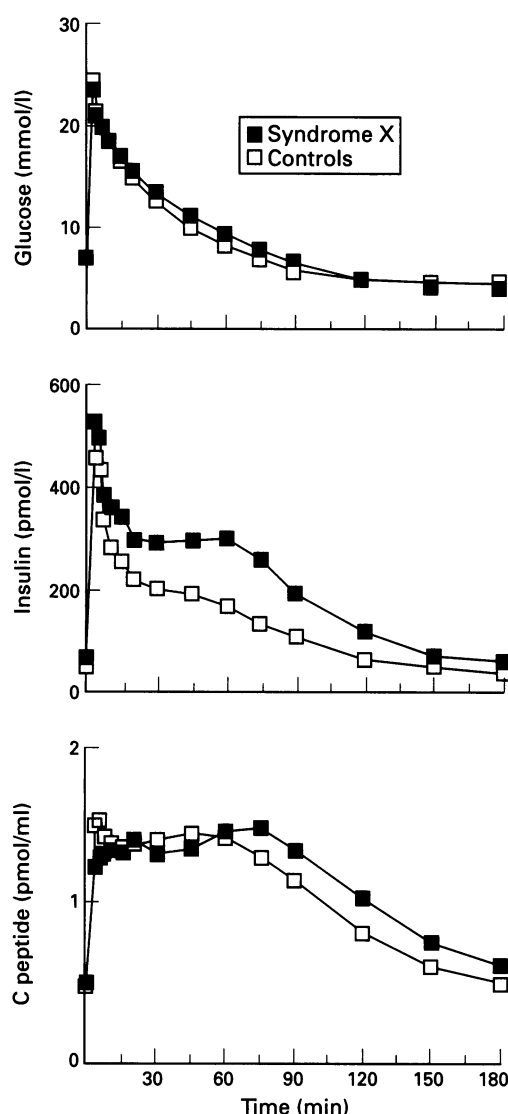
Cases and controls were well matched for age, weight, and body mass index (table 1). Mean systolic blood pressure was significantly higher in the syndrome X group ( $p < 0.01$ ), with no difference in diastolic values (table 1). The syndrome X men had higher mean triglyceride concentration together with lower HDL cholesterol and apolipoprotein AI concentrations (table 2). There were no differences between the groups for concentrations

Table 3 Insulin and carbohydrate

	Syndrome X	Controls	p Value
Fasting insulin* (pmol/l)	70.1 (+7.9, -7.3)	53.8 (+4.2, -3.6)	<0.05
Fasting glucose (mmol/l)	5.4 (0.1)	5.3 (0.1)	NS
Incremental insulin area (10 <sup>4</sup> min. pmol/l)*	2.46 (+0.40, -0.34)	1.56 (+0.11, -0.10)	<0.001
First phase insulin area (10 <sup>4</sup> min. pmol/l)*	0.31 (+0.06, -0.05)	0.32 (+0.03, -0.03)	NS
Second phase insulin area (10 <sup>4</sup> min. pmol/l)*	2.08 (+0.37, -0.31)	1.17 (+0.11, -0.10)	<0.001
First phase C-peptide area (min. mmol/l)*	5.7 (+1.0, -0.9)	6.9 (+0.7, -0.6)	NS
Second phase C-peptide area (min. mmol/l)*	96 (+14, -13)	87 (+5, -5)	NS

\*Log or square root transformed data result in asymmetric SEMs. Values are mean (SEM).

Figure 1 Mean plasma concentration profiles for blood glucose, insulin, and C-peptide before and after a 0.5 g/kg intravenous glucose load.



of total cholesterol, LDL cholesterol, apolipoprotein B, or lipoprotein (a) (table 2).

Fasting plasma glucose concentrations were similar in both groups despite a significantly higher fasting insulin concentration in the syndrome X group ( $p < 0.05$ , table 3). Figure 1 shows plasma concentration profiles for glucose, insulin, and C-peptide during the IVGTT. A greater insulin response was seen in men with syndrome X, but plasma glucose and C-peptide responses were similar. A greater second phase response was responsible for the higher mean incremental area in the syndrome X group as no significant difference in first phase response was seen (table 3). Mean (SEM) insulin sensitivity ( $S_i$ ) was lower in the syndrome X group ( $3.40 (+0.61, -0.56) v 4.95 (+0.40, -0.38) \times 10^{-5} \text{ min}^{-1}/(\text{pmol/l})$ ,  $p < 0.05$ , fig 2).

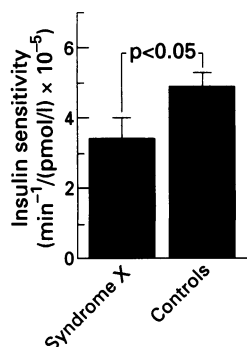


Figure 2 Insulin sensitivity derived from the minimal model in men with syndrome X and controls.

## Discussion

These men with cardiological syndrome X have all the characteristic features of the insulin resistance syndrome: hyperinsulinaemia, increased triglyceride concentrations, decreased HDL cholesterol concentrations,

and raised blood pressure compared with healthy men. Earlier work has shown that insulin resistance and hyperinsulinaemia are associated with increased plasma triglycerides and low plasma HDL cholesterol.<sup>17,18</sup> Similarly, a close relation between blood pressure and insulin resistance has been described in both hypertensive and normotensive persons.<sup>17,19</sup> It has been suggested that the insulin resistance syndrome may be associated with the development of atherosclerosis and coronary heart disease.<sup>7</sup>

A recent study has also shown insulin resistance, by the euglycaemic clamp method, in 11 patients with syndrome X compared with nine controls with non-cardiac chest pain.<sup>20</sup> By contrast with our findings, these authors failed to show significant differences in serum cholesterol, triglycerides, HDL cholesterol, or blood pressure. Mean serum HDL cholesterol concentration was, however, 12% lower and mean serum triglycerides 14% greater in the syndrome X group, findings consistent with the insulin resistance syndrome.

In our study we excluded those with hypertension, diabetes, obesity, and other known insulin resistant states.<sup>19,21,22</sup> Furthermore, the groups were closely matched for body mass index and age, both of which have been reported to affect sensitivity to insulin.<sup>23,24</sup> Smoking has been reported to increase insulin resistance<sup>25</sup> but cannot be responsible for our findings as there was a similar proportion of previous smokers in each group, with more current smokers in the control group. The difference in previous and current smoking habits probably reflects clinical advice given to patients with chest pain. The difference found in insulin resistance is likely to relate to the diagnosis of syndrome X. Although our study could not find a causative role for the insulin resistance syndrome in syndrome X, the similarity of metabolic profile between syndrome X and atherosclerotic coronary heart disease suggests a common aetiology or common underlying pathology.

The insulin resistance found in these men with syndrome X was associated with both fasting and stimulated hyperinsulinaemia despite a normal fasting blood glucose concentration and normal glucose tolerance. We divided the hyperinsulinaemic response to glucose into first phase, representing mainly secretion of stored insulin, and second phase, representing the end result of later insulin production and elimination. In the syndrome X group the hyperinsulinaemic response was mainly second phase, with no significant differences in first phase insulin area. There were no significant differences in either first or second phase C-peptide response suggesting that increased pancreatic secretion alone does not account for the increased insulin response in these patients and that altered insulin elimination may be contributory.

Myocardial ischaemia is thought to be a feature of cardiological syndrome X and has been shown by a number of alternative methods as well as the exercise electrocardiogram

used in our study. These have included reduced coronary perfusion<sup>26,27</sup> and inducible ischaemia as assessed by production of coronary sinus lactate.<sup>26,28</sup> At present, obstructive atheromatous disease has not been shown in the coronary arteries of patients with syndrome X. The larger epicardial vessels have, by definition, been shown to be clear at coronary angiography, and myocardial biopsy has excluded atherosclerosis in the very small myocardial vessels.<sup>26,29</sup> Neither angiography nor biopsy, however, allows visualisation of the important intermediate size vessels (about 45–150 µm in diameter). These arteries could conceivably be the site of atherosclerosis responsible for ischaemia and angina in syndrome X.

The finding of myocardial ischaemia in syndrome X does not necessarily mean that the chest pain must be caused by obstructive coronary atheroma. The most likely cause of ischaemia without coronary atherosclerosis would be a functional impairment of coronary vasodilatation. Insulin resistant states, such as diabetes and hypertension, have been linked with reduced activity of endothelium dependent relaxing factor.<sup>30,31</sup> Insulin has also been shown to stimulate smooth muscle cell proliferation in humans.<sup>32</sup> Such mechanisms may contribute to an abnormal vasoconstrictive response in syndrome X leading to ischaemia.

Our data show that syndrome X is an insulin resistant state, exhibiting all the features of the insulin resistance syndrome. To what extent these abnormalities relate to the cause of the symptoms remains unknown and is an important area for further investigation.

JWS is supported by a Bristol-Myers Squibb Cardiovascular Research Fellowship. We thank Dr Christopher Ley for help with patient recruitment, Mary Miller and Lee Rogers for assistance with clinical procedures, and Anthony Proudler, Carl Felton, and Melek Worthington for insulin, C-peptide, and lipoprotein assays.

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